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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,557	GODDARD ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 6 has been canceled.

Claim 1 has been amended.

2. Claims 1-5 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

4. The rejection of claims 1-5 under 35 U.S.C 101 because the claimed invention is not supported by a substantial asserted utility or a well-established utility is maintained.

The response filed 10/14/2005 has been carefully considered, but is deemed not to be persuasive. Applicant again reviews the evidentiary standard regarding the legal presumption of utility. The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of utility. Applicant argues again that the utility need not be proved to a statistical certainty, a reasonable correlation between the evidence and the asserted utility is sufficient and applicant cites numerous case law in support of applicants arguments that for a therapeutic and diagnostic use, utility does not have to be established to an absolute certainty and the evidence need not be direct evidence so long as there is a reasonable correlation between the evidence and the asserted utility. In response to these arguments, the examiner agrees with Applicant's statement that absolute certainty is not the legal standard for utility. However, the rejection does not question the presumption of truth, or credibility, of the

asserted utility. The asserted utilities of cancer diagnostics and cancer therapeutics for the claimed polypeptides are credible and specific, however, they are not substantial. The data set forth in the specification are preliminary at best because the specification does not teach the expression of the PRO1069 polypeptide nor any particular biological activity of the polypeptide. Applicant summarizes their arguments and the disputed issues involved. Applicant reiterates that Example 18 in the specification shows that mRNA encoding the PRO1069 polypeptide is more highly expressed in normal kidney compared to kidney tumor and applicant asserts that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein and based on the identification of the mRNA encoding the PRO1069 polypeptide under-expressed in tumor tissue compared to normal tissue renders the PRO1069 polypeptide useful as a diagnostic tool for the determination of the presence or absence of tumor. In support, applicant again argues with the declaration of J. Christopher Grimaldi (previously submitted as Exhibit 1) that there is at least a two-fold difference in PRO1069 mRNA between kidney tumor and normal kidney tissue. This has been fully considered, but is not found persuasive. First, it is important to note that the instant specification provides no information regarding PRO1069 polypeptide levels in tumor samples relative to normal samples. Only gene expression data is presented. The declaration does not provide factual data such that the examiner can independently draw conclusions. There is no evidentiary support to Dr. Grimaldi's statement that if a difference in gene expression is detected, this indicates that the gene and its corresponding polypeptide

and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor. Further, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al (Journal of Proteome Research 2:405-412, 2003, Ids reference 23 filed 3/31/2005) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Further Dr. Grimaldi has an interest in the present case as he is an invention in the present application and is employed by the assignee. Applicant is reminded that in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Applicant argues Hu et al (2003, Journal of Proteome Research 2:405-412, of record) as being based upon a statistical analysis of information from published literature rather than from experimental data. Applicant characterizes Hu et al as being limited to estrogen-receptor-positive breast tumor only. Applicant criticizes the types of statistical tests performed by Hu. Applicant concludes that, based on the nature of the statistical analysis performed in Hu, and the fact that Hu only analyzed one class of genes, the conclusions drawn by the examiner are not reliably supported. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on the presumption that increased mRNA production leads to increased protein production. Hu is directly on point by showing that this presumption is incorrect when designating protein as diagnostic markers for cancer. Hu analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between the samples

(emphasis added; 2003, Nature Biotechnology 21(9):976-977). The instant specification does not disclose that PRO1069 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu, the skilled artisan would not reasonably expect that PRO1069 protein can be used as a cancer diagnostic. Additionally, Hanna J. S. et al (Pathology Associates Medical Laboratories, 1999) show that gene amplification does not reliably correlate with polypeptide over-expression, and thus, the level of polypeptide expression must be tested empirically. The instant specification does not provide additional information regarding whether or not PRO1069 polypeptide is more highly expressed in normal kidney tissue compared to kidney tumor, and thus, the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. MPEP 2107 I states:

> A "substantial utility defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the specification does not disclose further testing of PRO1069 gene product expression levels. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products based on the claimed invention are not in "currently available" form, the asserted utility is not substantial.

Regarding Applicant's criticism of Hu et al's statistical analysis, Applicant is holding Hu et al to a higher standard than their own specification, which does not

provide proper statistical analysis such as reproducibility, standard error rates, etc. Regarding Applicant's criticism of Hu et al as being limited to a specific type of breast tumor, Hu et al is cited as one of several pieces of evidence that gene expression in a tumor does not correlate protein expression. Considering the evidence of record as a whole, there is no reasonable correlation between mRNA levels and protein levels.

Applicant reiterates that it is well established in the art is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein and applicant argues again with the previously submitted second declaration of J. Christopher Grimaldi (previously submitted as Exhibit 2), which states that those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed ...the gene product or polypeptide will also be over-expressed and this same principle applies to gene under-expression. Further, applicant argues again with the declaration of Dr. Paul Polakis (previously submitted as Exhibit 3) which states that based upon his experience accumulated in more than 20 years of research, that it is his scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase of the encoded protein in the tumor cell relative to the normal cell and that based on his experience although reports exist where such a correlation does not exist, such reports are exceptions to a commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein and applicant cites Alberts [a] (4^{th} ed. 2002; Exhibit 2), Alberts [b] (3^{rd} ed. 1994; Exhibit 1), Lewin and Zhigang for support that mRNA expression correlates with protein expression. The declarations of

Dr. Grimaldi and Dr. Polakis and applicant's arguments have been fully considered, but are not found persuasive. Again, Alberts [b] and Lewin actually support the fact that further research would have to be carried out to determine if the polypeptide expression levels track with the expression levels of the corresponding mRNA. Alberts and Lewin show that there are several levels that control gene expression both at the transcriptional (i.e., mRNA synthesis) and the translational (i.e., protein production) levels, which appears to be acknowledged by Applicant. Thus, one skilled in the art would not accept that increased mRNA levels directly correlate with the level of the corresponding polypeptide in view of the multitude of controls at the transcriptional and translational levels. With respect to applicant's arguments regarding the art of Zhigang et al, again the Examiner agrees that statistical certainty is not required, however, Zhigang support that one needs to actually determine the expression of the protein to be sure of expression given the disparate regulation of gene expression and protein expression, which don't even occur in the same cellular compartment. Applicant also argues that Alberts [a] (4th ed. 2002; Exhibit 2). figure 6-3 on page 302 illustrates the general principle that there is a correlation between increased gene expression and increased protein expression. In response to this argument, while increased transcript levels can lead to increased polypeptide levels, there are other regulatory factors that also effect the rate of translation as evidenced by Alberts [b] (Exhibit 1) in Figure 9-72. Additionally, Meric et al (Molecular Cancer Therapeutics, 1:971-979, 2002, Ids reference 17, filed 3/22/2005) teaches that in addition to variations in mRNA sequences that increase or decrease translational efficiency, changes in the expression or

availability of components of the translational machinery (i.e., over-expression of eIF4E, eIF4G, eIF-2α, eIF-4A1, ect...) as well as activation of translation through aberrantly activated signal transduction pathways also effect the rate of translation in cancerous cells. Figure 6-3 of Exhibit 2 (Alberts, 4th ed. 2002) does not account for these other types of controls that exist in cancerous cells. Applicant argues that Meric et al supports the assertion that the regulation of mRNA levels is the predominant mechanism of control for the majority of genes as Meric states "[t]he fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells." (Meric at pg. 971). Applicant states that if there were no general correlation between differences in mRNA and differences in protein, there would be no reason to study changes in mRNA. In response to these arguments, it is reiterated that Meric indicates most efforts have concentrated on gene expression at the mRNA level due to the advent of cDNA array technology, which facilitated this type of analysis. Further, Meric et al in agreement with Alberts and Lewin acknowledges that gene expression is quite complicated and is regulated at the level of mRNA stability, mRNA translation and protein stability. Also, Greenbaum et al in agreement with Meric evince that the focus of studies on mRNA rather than protein in the literature is due to the more copious and technically easier mRNA experiments (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8). Specifically, Greenbaum cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations

between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. Again, Applicant acknowledges that gene transcription is not the only point of regulation, but maintains that gene transcription is the predominant point of regulation.

Further, applicant argues that the statement of Jang et al (Clinical and Experimental Metastasis, 15:469-483, 1997, abstract, of record) that "further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells." is simply an indication that

further research could be performed to evaluate whether the genes of interest are regulated at the predominant point of regulation (transcription) or whether a less common point of regulation is utilized. Again, applicant appears to acknowledge that regulation occurs at both the transcriptional and translational levels and are distinct, which supports the lack of a substantial utility in the present application, i.e., further research is required to confirm PRO1069 polypeptide expression. Jang's statement that "further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells." evinces that further research would be required to determine if protein levels track with levels of the corresponding mRNA.

Applicant argues that Gygi (Molecular and Cellular Biology, 19(3):1720-1730, March 1999, of record) provides strong evidence in support of a general correlation between mRNA and protein levels, indicating that the correlation is especially strong for highly expressed mRNAs. Considering that Example 18 of the present specification shows higher expression of PRO1069 mRNA in normal kidney compared to tumor. First, "highly and "more highly" expressed is relative in nature and it is unclear to what extent the PRO1069 mRNA is "more highly" expressed as the specification does not quantitate the expression level or provide a proper statistical analysis for reliability, reproducibility, ect... Further, Gygi clearly states "We found that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant

steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold." (see abstract).

In response to the art of Hanash S. [a] (Nature Reviews, Applied Proteomics Collection, pp. 9-14, March 2005, of record) and Hanash et al [b] (The Pharmacogenomics Journal, 3(6):308-311, 2003, of record), Applicant again acknowledges that gene expression is regulated at numerous levels, however, applicant maintains that the declarations and supporting evidence make it clear that regulation of mRNA levels is the predominant mechanism of control for the majority of genes. Again, in agreement with Gygi and Haynes, Hanash S. [a] (Nature Reviews, Applied Proteomics Collection, pp. 9-14, March 2005, of record) states "There is a need to profile gene expression at the level of the proteome and to correlate changes in gene-expression profiles with changes in proteomic profiles. The two are not always linked-numerous alterations occur in protein levels that are not reflected at the RNA level." (see page 12). Further, Hanash [a] teaches that tumors are complex biological systems and no single type of molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics (see abstract). Hanash et al [b] states "However perfected DNA microarrays and their analytical tools become for disease profiling, they will not eliminate a pressing need for other types of profiling technologies that go beyond measuring RNA levels, particularly for disease-related investigations." (see page 311). According to Hanash et al [b], there is a need to assay protein levels and activities and numerous alterations may occur in proteins that are not reflected in changes at the RNA level (see page 311). Further, Winstead states

"For all the information gene microarrays provide, they reveal relatively little about proteins, the molecules that carry out most of the functions of a cell. Gene arrays detect the presence of messenger RNA, the chemical involved in translating DNA into protein. Tracking this middle step in the production process reveals nothing about three areas of interest to researchers: protein function, the abundance of protein in a cell, and modifications to proteins after they are produced – changes that may be critical in the development of disease." (top of pg. 3) (Winstead E. R., Genome News Network, "The Evolving Art of Arrays", www.genomenewsnetwork.org, pp. 1-4, 15 September 2000). Irving et al (Nature Biotechnology 18:932-933, September 2000) state: "But despite their obvious value in gene expression profiling, such arrays reveal relatively little information about the final concentrations of gene products in a cell, and they reveal nothing about post-translational modifications, protein activity, and protein-protein interactions (pg. 932, top left column). In view of the totality of evidence, the skilled artisan would not reasonably presume that PRO1069 polypeptide is more highly expressed in normal kidney than kidney tumor based on the disclosure regarding "more highly expressed" PRO1069 mRNA without actually testing for PRO1069 polypeptide expression. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it requires further research to identify or confirm a "real world" use. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. This situation

is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct, 1966), in which the court held that

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license" "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicant again refers to three additional articles previously submitted by Applicant (Orntoft et al; Exhibit filed 8/16/2004, Hyman et al; Exhibit filed 8/16/2004, and Pollack et al: Exhibit filed 8/16/2004) as providing evidence that gene amplification generally correlates with levels of the encoded polypeptide. Applicant characterizes Orntoft et al as teaching mRNA and protein levels for individual genes located within amplified or deleted chromosomal regions and found that of the 40 proteins analyzed only one showed disagreement between transcript alteration and protein alteration (Orntoft, page 42). Applicant maintains that Orntoft's results demonstrate that in general, a change in mRNA level results in a change in the level of the encoded polypeptide and the correlation is independent of whether the increase in mRNA levels is a result of increased transcription rate or as result of an increase in the copy number of the gene. This has been fully considered, but is not found to be persuasive. Again, Orntoft appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Orntoft et al do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification

reports data regarding amplification of individual genes, which may or may not be in a chromosomal region, which is highly amplified. Orntoft et al concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (page 40). This analysis was not done for PRO1069 in the instant specification. Therefore, the relevance of Orntoft et al remains unclear. Hyman et al used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA over-expression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al also do not support utility of the claimed polypeptides. Pollack et al also used CGH technology, concentrating on large chromosome regions showing high amplification (page 12965). Pollack et al did not investigate polypeptide levels. Therefore, Pollack et al also do not support the asserted utility of the claimed invention. Importantly none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specifications assertions that the claimed PRO1069 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicant again asserts that the asserted utilities are specific (pg. 21-22 of the response). It is reiterated that the asserted utilities are credible and specific, however, they are not substantial for the reasons of record and reiterated above.

For these reasons the rejection is maintained.

5. The rejection of claims 1-5 under 35 U.S.C. 112, first paragraph, is maintained. Specifically, since the claimed invention is not supported by a substantial utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. The rejection of claims 1-5 under 35 U.S.C. 112, first paragraph, because the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response filed 10/14/2005 has been carefully considered, but is deemed not to be persuasive. The response maintains the position that while there are some exceptions, in general differential expression levels of mRNA leads to differential protein expression levels. Applicant concludes that the specification enables one skilled in the art to make and use the claimed invention. Again, as discussed above in the utility rejection the art of Alberts, Lewin, Meric, Jang et al, Vallejo et al, Powell et al, Fu et al, Gygi et al, Haynes et al, Hanash S [a], Hanash et al [b], Winstead and Irving et al underscores the unpredictability in the art and the predictability of protein translation and its possible use as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Applicant has not submitted any evidence or pointed to evidence already of record that the experimentation required to use the PRO1069 antibodies for cancer

diagnosis would be merely routine in view of the unpredictability in the art, the lack of guidance and direction in the specification as it pertains to using PRO1069 antibodies as a diagnostic tool and the absence of exemplary guidance. In view of the totality of evidence of record, it would require undue experimentation to reasonably use the antibodies of the present claims as a diagnostic or therapeutic agent with a reasonable expectation of success.

Priority

Applicant claims priority to five previous applications in the preliminary amendment of 09 September 2002. Priority is granted to PCT/US00/23328, filed 24 August 2000, as the disclosure of '328 is identical to the instant disclosure. However, priority is not granted to USSN 09/380,137, PCT/US99/12252 and 60/088,740 since these applications do not disclose the quantitative PCR analysis of a cDNA library measuring mRNA expression (and not microarray analysis) upon which applicant relies for utility of the instantly claimed polypeptides. Therefore, the filing date for the purpose of art rejections is deemed to be 24 August 2000. Applicant is reminded that benefit to a prior-filed application requires written description and enablement under the first paragraph of 35 U.S.C. 112.

7. The rejection of claims 1-2 and 4-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Lal et al (WO 00/00610, 1/6/2000, cited previously on PTO-892 mailed 4/15/2004) is maintained.

The response filed 10/14/2005 argues as previously with the Stempel Doctrine. Applicant states that they were in possession of so much of the claimed invention as is disclosed in WO 00/00610 prior to the filing date of WO 00/00610. Applicant also submits a Declaration under 37 CFR 1.131 by Goddard et al to establish prior invention of the claimed subject matter prior to Lal's earliest priority date of 6/26/98 and thus, Lal et al is not available as priori art. This has been fully considered but is not found persuasive. As an initial matter, the instant rejection was made under 35 U.S.C. 102(a) as of the publication date, i.e., 1/6/00. Thus, applicant's arguments pertaining to Lal's first provisional application relating to SEQ ID NO:50 are not relevant. With respect to the Stempel Doctrine, as discussed above (see "*Priority*"), the filing date for the purpose of art rejections is deemed to be 24 August 2000 because prior applications USSN 09/380,137, PCT/US99/12252 and 60/088,740 do not disclose the quantitative PCR analysis of a cDNA library measuring mRNA expression. Applicant is reminded that benefit to a prior-filed application requires written description and enablement under the first paragraph of 35 U.S.C. 112. The priority documents do not provide adequate written support for the quantitative PCR analysis of a cDNA library measuring mRNA expression (i.e., Example 18). For these same reasons, the Declaration of Goddard et al filed on 10/14/2005 under 37 CFR 1.131 has been considered but is ineffective to overcome the Lal et al reference.

8. The rejection of claims 1-2 and 4-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Walker et al (U.S. Patent 6,277,574 B1, 4/9/1999) is maintained.

The response submits a Declaration under 37 CFR 1.131 by Goddard et al to establish prior invention of the claimed subject matter prior to April 9, 1999. Based on the supplied evidence, Applicant concludes that Walker et al is not available as prior art. The Declaration of Goddard et al filed on 10/14/2005 under 37 CFR 1.131 has been considered but is ineffective to overcome the Walker et al reference. As discussed above (see "*Priority*") the filing date for the purpose of art rejections is deemed to be 24 August 2000 because prior applications USSN 09/380,137, PCT/US99/12252 and 60/088,740 do not disclose the quantitative PCR analysis of a cDNA library measuring mRNA expression. Applicant is reminded that benefit to a prior-filed application also requires written description and enablement under the first paragraph of 35 U.S.C. 112.

9. The rejection of claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker et al (U.S. Patent 6,277,574 B1, 4/9/1999) in view of Queen et al (U.S. Patent 5,530,101, issued 6/96, cited previously on PTO-892 mailed 4/15/2004) is maintained.

Applicant argues as above for Walker, i.e., Applicants have demonstrated conception of the claimed invention prior to April 9, 1999 and diligence in reducing the invention to practice. Applicant concludes that Walker is not available as prior art. Again, the Declaration of Goddard et al filed on 10/14/2005 under 37 CFR 1.131 has been considered but is ineffective to overcome the Walker et al reference. As discussed above (see "*Priority*") the filing date for the purpose of art rejections is deemed to be 24 August 2000 because prior applications USSN 09/380,137,

PCT/US99/12252 and 60/088,740 do not disclose the quantitative PCR analysis of a cDNA library measuring mRNA expression. Applicant is reminded that benefit to a prior-filed application also requires written description and enablement under the first paragraph of 35 U.S.C. 112.

Conclusions

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at

(571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

SHEELA HUFF
PRIMARY EXAMINER